PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

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DUE DATE:	—
FORMALITIES:	HISL ✓
PAT. OFF:	LRC /F
ON DB:	—
CASE NO:	P20282-PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	26.11.2004
Applicant's or agent's file reference: PZ0282-PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/04573	24.10.2003	25.10.2002

Applicant: AMERSHAM PLC

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Oberhauser, A Tel. +49 89 2399-8139

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PZ0282-PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/04573	International filing date *(day/month/year)* 24.10.2003	Priority date *(day/month/year)* 25.10.2002
International Patent Classification (IPC) or both national classification and IPC A61K51/08		
Applicant AMERSHAM PLC		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1-5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31.03.2004	26.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Veronese, A Telephone No. +49 89 2399-7824

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/04573

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-37 as originally filed

Claims, Numbers

1-28 received on 22.10.2004 with letter of 20.10.2004

Drawings, Sheets

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 28 (IA)

   because:

   ☒ the said international application, or the said claims Nos. 28 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 28 (IA)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-28
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-28
Industrial applicability (IA)	Yes:	Claims	1-27
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 28 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). However, although not required under the provisions of the PCT, an opinion will be given with respect to novelty and inventive step.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents; unless otherwise indicated, reference is made to the relevant passages emphasized in the Search Report:

D1: WO 02 070018 A (MENDIZABAL MARIVI ;AMERSHAM PLC (GB); 12 September 2002
D2: WO 01 77145 A (INDREVOLL BAARD); NYCOMED IMAGING AS (NO)) 18 October 2001
D3: WO 99 60018 A (MENDIZABAL MARIVI); GIBSON ALEX (GB); CHAMP) 25 November 1999
D4: WO 01 89584 A (KLAVENESS JO ;NYCOMED IMAGING AS (NO)) 29 November 2001
D5: WO 02 26776 A (CUTHBERTSON ALAN ;NYCOMED IMAGING AS (NO)) 4 April 2002

NOVELTY (Art.33(2) PCT))

The present invention is based on the discovery that, when technetium complexes of compounds having formula (I) are prepared, if the reaction temperature is simply left at room temperature, transient kinetic forms of the complex are formed as by-product, together with the desired thermodynamic product.
The inventors have also discovered that other undesired lipophilic species can be formed in the course of the complexation reaction, especially when elastomeric rubber stoppers are used to close the reaction vials.
The inventors have now found that the formation of kinetic species can be avoided if the reaction mixture is heated, and that the formation of lipophilic species can be reduced if the use of elastomeric rubber stoppers is avoided. Accordingly, the inventors propose to carry out the complexation reaction under conditions in which the formation of undesired species is minimized. Based on this discovery, the present application claims products comprising the technetium complexes of formula (I) comprising the kinetic and the lipophilic species in very reduced amounts.

D1 (WO02070018, see compounds at pages 19, 20) discloses compositions comprising Tc chelates as in claims 1,11 of the present application conjugated with peptide sequences. The use of these compounds for imaging is also disclosed. These compositions comprise, as additional ingredients an organic acid (ascorbic acid) and a radioprotectant (para-aminobenzoic acid).
Experiments 7 and 9 show that upon radio labelling a transient Tc complex is formed, which converts to the stable complex form in few hours. The stable form has been isolated in pure form. Experiment 9 reports the radio labelling of the chelate at different temperatures (up to 75 degrees). According to the inventors of the present application, at this temperature all the transient complex convert to the stable thermodynamic form. It is assumed therefore that no kinetic product was present in the product formed according to examples 7 and 9.
D1 does not explicitly mention the use of elastomeric rubber stoppers, and at the moment it may not be excluded that such stoppers have been used, and that lipophilic species were present in the crude reaction mixture. However, experiments 7 and 9 indicate that the different complexes present in the reaction mixture were resolved with HPLC, and that pure samples of each of the different species were obtained.
The inventors state in the description of the present application that the lipophilic impurities are retained very strongly by the reverse stationary phase used for the HPLC (see page 9 last paragraph - page 10 first paragraph), and that they can be eluted from the column only if extreme conditions are used. It is therefore reasonable to assume that, if lipophilic impurities were present in the crude reaction mixture of examples 7 and 9, these impurities have been removed by the HPLC purification mentioned in these examples.
In view of this prior art, the subject matter of claims 1-5,11-12,14-28 is not new in the sense of Art.33(2) PCT.

D2 (WO0177145, see example 2, 2f, 2g and 1e) discloses compositions comprising Tc chelates of structure as in claims 1, 11 conjugated with peptide sequences, and their use for imaging applications. According to the statement at page 42, line 20-22, the complexes can be obtained heating the mixture at 75 C. Even if this passage refers back to example 1e), the inevitable consequence of this statement is that also the labelled derivative has been disclosed. Also in this case, the presence of the kinetic derivative is to be excluded and any lipophilic impurity, if present in the crude mixture would have been removed by the final purification step by HPLC. In view of this prior art, the subject matter of claims 1-5,11-12,16-23 is not new.

Chelating agents of formula I and II, comprising an antiplasmin peptide are already

known from **D3** (WO9960018, see compounds 5 and 6 and example 11). These compounds have been labelled at room temperature; the presence of transient kinetic products and of lipophilic products in the crude reaction mixture may not be excluded. However page 22, lines 26 - page 23, line 3 also refer to HPLC purification of the labelled product. A gradient "system B" was used. From the statement in the present application at page 9, line 22- page 10, line 3 and at page 12, lines 1-4, it appears that such purification step would have removed the transient and the lipophilic impurities from the desired product. In view of this prior art, it appears therefore that also the subject matter related to the specific antiplasmin derivatives of claims 6-10, 13 is not new.

Note 1: claim 19 is directed to a kit comprising the ligand of formula (I); since this claim only refers to the ligand, and not to the purity of the compositions of claim 1, it is even broader in scope. This claim may thus not be considered new over the above mentioned documents, independently from any reasoning concerning purity requirements.

Note 2: as already mentioned above, the present invention is based on the discovery that certain impurities are formed when chelating agents of formula (I) are labelled with technetium. Based on this discovery, the inventors have invented a process to label the compounds avoiding, at least in part, the formation of impurities. This method appears to be new and to involve an inventive step.
Products (here pure compositions) obtainable using this method may however only be considered new if the claimed compositions have not been obtained using any of the methods disclosed in the prior art. In the present case, it appears that compositions comprising the pure thermodynamic Tc complex of formula (I) have been prepared using the methods disclosed in documents **D1-D3**. The fact that these documents have not explicitly mentioned the final pure products is here irrelevant to establish novelty.

INVENTIVE STEP

Most of the claimed subject appears not to be new over the prior art. The subject matter which is still new (for example subject matter relating to the combinations of certain specific ligand structures, and to the presence of further ingredients) is not characterized by any technical feature producing any new unexpected technical effect. For this reason, the subject matter of the claims which is still new may not be considered to involve an inventive step in the sense of Art.33(3) PCT.

INDUSTRIAL APPLICATION

For the assessment of the present claim 28 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.